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APPELLANTS' REPLY BRIEF Responsive to Examiner's Answer Mailed May 18, 2007 Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	RICE-012
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	First Named Inventor	DALY, ROGER J.
	Application Number	09/509,196
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	Group Art Unit	1649
	Examiner Name	CHERNYSHEV, O.
	Title: "A POTENTIAL EFFECTOR FOR THE GRB7 FAMILY OF SIGNALLING PROTEINS"	

Sir:

This Reply Brief is in response to the Examiner's Answer mailed by the Office on May 18, 2007.

The Commissioner is hereby authorized to charge deposit account number 50-0815 to cover any fee required under 37 C.F.R. §1.17(c) for filing Appellants' reply brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-0815.

REPLY BRIEF

In this Reply Brief, Appellants address specific assertions and comments made in the Examiner's Answer mailed May 18, 2006. Appellants note that all arguments previously presented still apply with equal force, but are not reiterated here solely in the interest of brevity and for the convenience of the Board.

The rejections of the claims under § 101 and §112, ¶1 are based on the Examiner's erroneous position that the claimed 2.2412 protein[1]-encoding polynucleotides do not have a patentable utility. In response, Appellants have traversed and asserted that the 2.2412 protein encoded by the polynucleotides of the claims has at least the following utilities:

1. Use of the 2.2412 protein (encoded by the polynucleotides of the present claims) as a reagent to detect Grb7 and Grb14;

The specification as filed discloses that 2.2412 protein specifically binds Grb7 and Grb14. As illustrated by pre-filing, post-filing and declaration evidence, Grb7 and Grb14 are known to be differentially expressed in certain cancerous cells as compared to non-cancerous cells of the same tissue type. Given this knowledge in the art, the ordinarily skilled artisan would recognize that the 2.2412 protein is useful to detect Grb7 and Grb14 levels in, for example, a tissue sample, to detect the presence of cancerous cells and facilitate a diagnosis.

2. Use of the 2.2412 protein and protein-encoding polynucleotides in detection of cancerous cells in view of the differential expression of 2.2412 in certain cancerous cells as compared to non-cancerous cells

This utility is asserted in the specification as filed; and is supported by post-fling evidence in the form of the Declaration of Yasumichi Hitoshi Under 37 CFR §1.132 (the "Hitoshi Declaration")

[1] Appellants note that the claims recite "polypeptide". However, solely for clarity the term "protein" is used interchangeably in the Brief, since this is the term used by the Examiner.

Appellants address below particulars errors in the May 18th Answer.

The Examiner Has Erred In Requiring That Appellants Prove Their Statements of Utility Unequivocally

The Examiner has erred in requiring that Appellants prove their statements in support of utility of the claimed invention under §101 with unequivocal evidence. As pointed out in Appellants' brief, such a requirement amounts to application of a standard *higher* than the preponderance of the evidence standard that is proper in the context of utility rejections. Appellants are not required to prove their utility unequivocally. Examples of the Examiner's errors in this regard are addressed below.

The Examiner has erred in demanding that 2.2412 protein exclusively bind Grb7 and Grb14

For example, the Examiner asserts that 2.2412 protein must *exclusively* bind to Grb7 or Grb14 in order for the 2.2412 protein to facilitate detection of a cancerous cell by detection of Grb7 and Grb14, and concludes "it is not clear and is not explained in the instant specification, as filed how 2.2412 could be used as a cancer marker based on its binding ability."[2]

The Examiner has demanded evidence to support an asserted utility that is far beyond that required by the law. Indeed, under such an exacting stand, an antibody that exhibited any cross-reactivity in binding to an antigen other than its target antigen would not be "useful". This is, of course, simply not the case. A protein (such as an antibody) exhibits sufficiently specific binding to make it useful in detecting a target protein (such as an antigen) so long as binding to the target protein is at a greater specificity than binding to a non-target protein.

The 2.2412 protein encoded by the polynucleotides recited in the present claims exhibits such sufficiently specific binding. Indeed, if the 2.2412 protein did not have this specific binding property, it would have never been isolated, since the 2.2412 protein was identified *based on its binding to Grb14*.[3]

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[2] May 12th Answer at page 11.

[3] Nucleic acid encoding the 2.2412 protein was identified in a yeast two-hybrid screen, using Grb14 as

However, this is not the sole evidence for Grb14 binding upon which Appellants rely. Appellants further characterized the binding activity of the 2.2412 protein. In the specification at page 10, line 26 to page 11, line 10, Appellants generated fusion proteins containing either a full length 2.2412 protein, an N-terminal portion of 2.2412 protein, or a C-terminal portion of 2.2412 protein. The fusion proteins were purified and immobilized on beads. The immobilized fusion proteins were then incubated with *lysates* from cells expressing a Grb14 fusion protein (which contains a tag to facilitate detection) or with *lysates* from human breast cancer cells expressing high levels of Grb7. Following incubation of the immobilized 2.2412 fusion protein with the Grb14-containing or Grb7-containing cell lysates, the samples were washed and bound proteins detected using an antibody that detected bound Grb14 fusion protein or bound Grb7. Appellants showed that *the 2.2412 protein bound specifically to both Grb14 and Grb7.*[4] Appellants also showed that The N-terminus of the 2.2412 protein bound more strongly to Grb14 and Grb7 than the C-terminus of the 2.2412 protein. These data demonstrate that 2.2412 protein binds Grb7 and Grb14 even in the presence of a cell lysate milieu, and binds with a specificity sufficient to withstand washing.

The Examiner has also erred in demanding that the asserted utility must be "explained in the instant specification". This is not required if the asserted utility is apparent to the ordinarily skilled artisan upon reading the specification. In the instant case, it was known that Grb7 and Grb14 were differentially expressed in human cancer cells. As discussed above, the specification shows that 2.2412 protein specifically binds Grb7 and Grb14. Indeed, the working example shows that 2.2412 protein binds Grb7 in a sample from a *human breast cancer cell. This is the very type of sample that could be used in a detection assay.* The specification thus provides adequate guidance and a working example as to how one could carry out detection of Grb7 in a breast cancer cell. Given the knowledge in the art and the disclosure of the instant specification, the person of ordinary skill in the art needs

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"bait". See the specification at page 6, line 28 to page 9, line 23.

[4] Specification at page 11, lines 3-5

nothing more to recognize that 2.2412 protein can be used to detect Grb7 and to detect Grb14.

The Examiner has erred in demanding that Grb7 and Grb14 expression be limited to certain cell types in order to support a utility of 2.2412 protein based on its binding to these proteins in cancer cells

In addition to the statements in the specification regarding Grb7 and Grb14 as targets to facilitate detection of cancerous versus non-cancerous cells, Appellants provided evidence in the form of pre-filing and post-filing publications. In response, the Examiner has taken the position that the evidence regarding Grb7 and/or Grb14 differential expression in cancerous cells is not sufficient. For example, the May 18th Answer at page 12 states:

> The prior art of record as presented in the articles cited by Appellant fails to support Appellant's statement that "Grb7 and Grb14 are recognized as markers for cancer at the time of filing of the present application" (top at p.8 of the Brief). Specifically, article by Daly (Cell Signal, 1998, 10, 613-618) presents data regarding tissue distribution of Grb7 and Grb14, which are disclosed as being highly expressed in wide variety of different normal tissues (p.614, second column).

The Examiner's logic is flawed. Appellants submit that whether a gene is expressed in a "wide variety of different normal tissues" is irrelevant. What *is relevant* is whether there are *differences in expression levels between cancerous cells and non-cancerous cells*. The publications submitted as evidence in the present case support that Grb7 and Grb14 indeed exhibit increased levels of expression in cancerous cells compared to non-cancerous cells.

The Examiner also states at page 12 of the May 18th Answer that:

> . Further, publication by Stein et al. (EMBO, 1994, 13, 6, 1331-40) discloses correlation between overexpression of Grb7 and ErbB2 in breast cancer cell lines as well as primary breast cancer specimens (p.615, first column); however, the article makes it clear that research data of Grb7 being associated with breast cancer was inconclusive at the time of publication: "[w]hether GRB-7 expression, like HER-2, has prognostic significance in patients with primary breast cancer remains to be seen. Although our data indicate a highly significant correlation between overexpression of HER-2 and overexpression of GRB-7 in patient samples, the relationship is imperfect; 24 out of the 34 specimens overexpression HER-2 also overexpressed GRB-7 but 10 do not".

In short, the Examiner has emphasized that the data in Stein et al. are in breast cancer cell lines, while at the same time seemingly ignoring that the rest of the very same sentence indicating that Stein et al. *also* discloses overexpression of Grb7 in primary breast cancer cells. The Examiner repeats this error in a long discussion of cancer cell lines in the text bridging pages 12-13 of the May 18th Answer. Moreover, the ordinarily skilled artisan would recognize that cancer cell lines are at least a *model* for cancer. Results obtained in cancer cell lines are not meaningless, as the Examiner seems to indicate.

The Examiner then construes Stein et al.'s statements in a manner that is overly negative. Stein et al. states that HER-2 and Grb7 expression are "highly significantly correlated" in 24/34 primary breast cancer samples. Just because Grb7 was not overexpressed in the other ten HER-2 "positive" samples does not undermine the utility of Grb7 expression in facilitating a cancer diagnosis. Indeed, the data of Stein et al. suggest that detection of increased Grb7 expression is an indicator of a cancerous state of a breast cell. If a breast cell has elevated Grb7 expression, more likely than not it is cancerous. Just because the *absence* of elevated Grb7 expression is not indicative of a non-cancerous cell does not render detection of Grb7 useless in facilitating a diagnosis of cancer. Indeed, if this is the

Examiner's position, then even HER-2, which is *not* overexpressed in every type of breast cancer, would have no utility.

It is rare in biology that there are "magic bullets" that can serve as a diagnostic. Instead, the complexities of biological systems normally require evaluating results of a single test in the context of other clinical signs and symptoms. There is no requirement that a test be "perfect" in order to be useful. If one had a breast lump as detected by mammogram, and the cells from a biopsy of that lump were elevated in expression for Grb7, then the clinician would have good reason to make a diagnosis of cancer.

The Examiner's position is not supported BY any court decision or guidelines

Nowhere in the law or in the guidance provided in the MPEP is there support for the Examiner's requirement of a "perfect" correlation to support a diagnostic utility. Instead, the law and the MPEP advises that general statements of diagnostic utilities are not sufficient. MPEP §2101.01 states:

> A general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed. Contrast the situation where an applicant discloses a specific biological activity and reasonably correlates that activity to a disease condition. Assertions falling within the latter category are sufficient to identify a specific utility for the invention.

In the instant case, Appellants' specification discloses that 2.2412 protein specifically binds Grb7 and Grb14. Expression of Grb7 and Grb14 was known at the time of filing to be elevated in human cancers, as exemplified by prostate and breast cancer. Appellants' specification provides a working example that show 2.2412 protein can be immobilized and used to detect Grb7 in primary human breast cancer cells. The requirements as set out in the MPEP have been met:

- the disease to be diagnosed is specified (human cancers, as exemplified by breast and prostate cancer); and
- the specific biological activity required has been demonstrated (specific binding to Grb7 from primary human breast cancer cells).

Appellants' burden under 35 USC §101 has been met.

Appellants' case is not like the case in *In re Fisher.*[5] As discussed in MPEP §2107.01, the claims of *Fisher* were directed to expressed sequence tags (ESTs), which are short nucleic acids the represent genes that are expressed in a cell and that can be used to discover what genes and downstream proteins are expressed in a cell. The court held that:

> the claimed ESTs can be used only to gain further information about the underlying genes and the proteins encoded for by those genes. The claimed ESTs themselves are not an end of [applicant's] research effort, but only tools to be used along the way in the search for a practical utility.... [Applicant] does not identify the function for the underlying protein-encoding genes. Absent such identification, we hold that the claimed ESTs have not been researched and understood to the point of providing an immediate, well-defined, real world benefit to the public meriting the grant of a patent.[6]

In contrast, Appellants have identified a function for 2.2412 protein *that is directly relevant to at least one of Appellant's asserted utilities, i.e., specific binding of 2.2412 protein to Grb7 and Grb14.* This is far more than the situation in *Fisher*, which provided nothing more than the sequence of certain polynucleotides expressed in maize.[7]

In addition, Appellants note that in the context of an asserted therapeutic or pharmacological utility, the courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition. For example, in *Cross v. Iizuka* the Federal Circuit commented on the significance of data from in vitro testing that showed

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[5] *In re Fisher*, 421 F.3d 1365, 76 USPQ2d 1225 (Fed. Cir. 2005).

[6] Id. at 1376, 76 USPQ2d at 1233-34).

[7] The application in *Fisher* disclosed that the five claimed ESTs could be used in a variety of ways, including: (1) serving as a molecular marker for mapping the entire maize genome, which consists of ten chromosomes that collectively encompass roughly 50,000 genes; (2) measuring the level of mRNA in a tissue sample via microarray technology to provide information about gene expression; (3) providing a source for primers for use in the polymerase chain reaction ("PCR") process to enable rapid and inexpensive duplication of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) con-trolling protein expression; and (7) locating genetic molecules of other plants and organisms. See *In re Fisher*, 421 F.3d at 1367-1368.

pharmacological activity:[8]

> We perceive no insurmountable difficulty, under appropriate circumstances, ***in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question***. Successful in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility.

(emphasis added)

Appellants submit that in view of the disclosure and the working example in the instant specification, the usefulness of 2.2412 protein in detecting Grb7 and/or Grb14 would be readily apparent to the ordinarily skilled artisan. Furthermore, similar to the therapeutic utility asserted for the compound in *Cross v. Iizuka*, the asserted diagnostic utilities for 2.2412 protein encoded by the polynucleotides of the present claims is sufficient to meet the requirements of 35 USC §101. The specification discloses successful *in vitro* testing demonstrating that immobilized 2.2412 protein specifically binds Grb7 and Grb14 in cell lysates prepared from *samples from human primary* cancer. Unlike the case in *Cross v. Iizuka*, the asserted diagnostic utility can be carried out in the same manner as disclosed in the instant specification. That is, the *in vitro* binding activity of 2.2412 protein demonstrated in the instant specification would be exploited in the asserted diagnostic utility *in vitro* – no further testing *in vivo* is required to establish that 2.2412 protein would have the desired binding activity. In this regard, the facts of the present case are not only parallel to those in *Cross v. Iizuka*, they present a situation that is less of a "leap" to the practical utility asserted.

For at least these reasons, Appellants respectfully request that the Examiner's rejections of the claims under 35 USC §101 and §112, ¶1 be reversed, and the claims passed to issuance.

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[8] *Cross v. Iizuka*, 753 F.2d 1040, 1051, 224 USPQ 739, 747-48 (Fed. Cir. 1985).

The Examiner Has Erred In Requiring That Extrinsic Evidence In Support of A Stated Utility Be Disclosed In The Specification

The May 18th Answer at page 14 the Examiner takes issue with the Kishi et al. and Tanaka et al. articles cited by Appellants in support of their statement of utility. The Examiner states:

> Further, articles of Kishi et al. and Tanaka et al. relate to coexpression and co-amplification of Grb7 in gastric and esophageal cancers, respectively. The instant specification, as filed, lacks any reference to an assertion of a specific utility of 2.2412 encoding polynucleotides in these types of cancer. Applicant is reminded that the patent law requires that the specific and substantial credible utility of the claimed invention must be fully disclosed at the time of filing.

Appellants submit that the specification points to prostate and breast cancers as *examples* of the types of human cancers in which Grb7 is differentially expressed. For example, the specification at page 5, lines 13-15 states:

> Grb7 family proteins exhibit differential expression in certain human cancers (particularly breast and prostate cancer) and may therefore be involved in tumour progression.

From this statement in the specification it is readily apparent that breast and prostate cancers are *exemplary* of the types of human cancers in which Grb7 is differentially expressed. Appellants supporting extrinsic evidence relating to differential expression of Grb7 in additional types of cancers, including gastric and esophageal cancers, is both relevant and appropriate. The Kishi et al. and Tanaka et al. publications are appropriate extrinsic evidence. This evidence need not be disclosed in the application as filed.[9]

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[9] *See, In re Hogan*, 194 USPQ 527, 537 (CCPA 1977) (holding that later publications that substantiate Applicant's assertions of utility or other art-related facts existing on the filing date are acceptable). The Examiner acknowledged this citation in the Final Office Action, but her only response to this and to all of Appellants' other arguments was a discussion of *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005).

The Examiner Has Erred In Characterizing and Considering The Evidence Of Record

The Examiner has made several statements in the May 18th Answer that indicate the Examiner has made statements regarding the evidence of record that are incorrect and has improperly dismissed extrinsic evidence submitted in support of Appellants' asserted utilities.

For example, the Examiner concluded that extrinsic evidence relating to differential expression of Grb7 in human gastric and esophageal cancers is not relevant to Grb7 expression human breast and prostate cancer. As discussed above in detail, this is incorrect since the specification makes clear that Grb7 is differentially express in human cancers *as exemplified by human prostate and breast cancer.*

The Examiner further errs in characterizing the evidence presented. For example, The May 18th Answer at page 14:

> The assertion that a novel polynucleotides encoding 2.2412 protein are useful as markers for prostate and breast cancer is not supported by any evidence of record presented in the instant specification or substantiated by reference to the prior art of record.

To the contrary, the Hitoshi Declaration provides data showing that 2.2412 protein is differentially expressed in human breast cancer cells.

The Examiner also errs in characterizing the data presented in the Hitoshi Declaration. The May 18th Answer at page 15 states:

> The Declaration presents additionally obtained information regarding expression of 2.2412 protein using Taqman assay, which shows that 2.2412 was expressed at higher levels in two types of lung cancer and in three types of breast cancer. First, the Declaration fails to explain how data related to lung cancer can support the specific utility of the instant molecules as markers for prostate cancer.

Appellants submit that the specification states that Grb7 is differentially expressed in certain human cancers, as exemplified by human breast and prostate cancers. The Appellants reasoned that the 2.2412 would also be differentially expressed, and thus has utility as a tumor marker. In view of this, the ordinarily skilled artisan would understand that the lung cancer data presented in the Hitoshi Declaration is relevant in support of this asserted utility, as lung cancer represents an additional type of cancer in which Grb7 is differentially expressed.

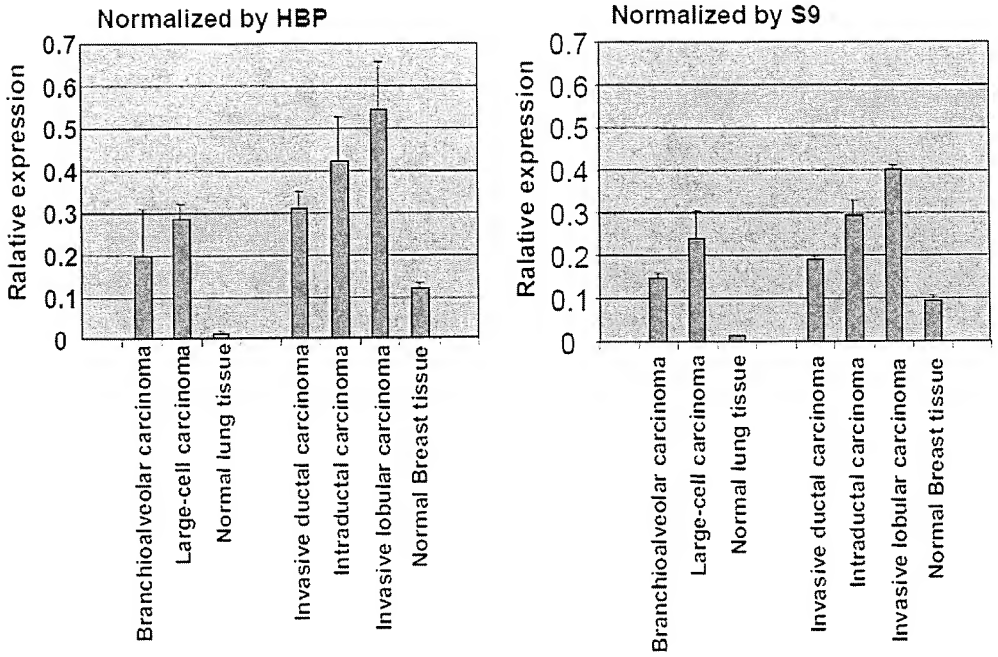
The Examiner has also erred in that she has confused what is required to support an asserted utility and *what might be required to support a claim to a method of diagnosis of cancer based on detecting 2.2412 expression levels*. The May 18th Answer continues in its analysis of the Hitoshi Declaration by stating at the text bridging pages 15-16:

Second, there is no disclosure of any specifics about "higher" levels, or critical levels of distribution, which are specifically associated with cancer pathology, or, alternatively, normal range of distribution. For example, if a clinician took a tissue sample from a alternatively, normal range of distribution. For example, if a clinician took a tissue sample from a patient with suspected breast cancer, what is the likelihood that when compared with normal tissue, the level of 2.2412 polynucleotides from the patient would be higher? How many samples would be needed? What sensitivity would be needed? Would the normal tissue have to be a pooled sample or could it be from a single individual?

First, to the extent the Examiner may assert that the data presented in the Hitoshi Declaration are not scientifically sound, Appellants point to Hitoshi Declaration at paragraph 13 where it states:

> Analysis was done in triplicate and standard errors for normal and tumor tissue were determined. Expression level in the matched samples were normalized to Ribosomal Protein s9 (S9) and the 23kD Highly Basic Protein (HBP).

The data presented in Exhibit 3 of the Hitoshi Declaration are reproduced below:



Thus, not only do the data in the Hitoshi Declaration normalized to expression levels using two different control genes, data showing 2.2412 expression in normal breast tissue and in normal lung tissue is provided. From this data it is also evident that 2.2412 expression is elevated .

Second, to the extent the Examiner is apparently requiring disclosure of "critical levels of distribution, which are specifically associated with cancer pathology", evidence that 2.2412 expression is present in *every breast cancer*, and guidance as to how to carry out a diagnostic method (e.g., number of samples, sensitivity required, use of pooled samples), the Examiner has again erred. These requirements the Examiner has imposed upon Appellants are not required by the law of utility. Indeed, the Examiner's grounds for rejection appear to be drawn to a situation where the claims at issue were directed to *a method of diagnosis* – the claims under appeal are not drawn to such methods.

Regardless, as discussed above, these requirements imposed by the Examiner are beyond the requirements of the law. For example, in order for a cancer diagnostic to be useful, it need not detect *all* cancers. Instead, it only need be that when, for example, a breast cancer cell exhibits elevated 2.2412 expression, this information can be used to facilitate a diagnosis of cancer. Appellants' asserted utility is that elevated 2.2412 expression can facilitate a diagnosis of cancer, ***not*** that

the *absence* of elevated 2.2412 expression indicates a cell is non-cancerous.

The Examiner also errs in characterizing the data set out in the Hitoshi Declaration. The May 18th Answer at page 16 states:

> The Declaration provides only limited information regarding the smallest representative number of samples, which appear to be taken from samples of different types of breast cancers. Therefore, the limited data presented in the Declaration regarding higher levels of 2.2412 in two types of lung cancer and in three types of breast cancer cannot support the asserted utility of the claimed molecules as markers for prostate and breast cancer.

As discussed above, the law (as exemplified in *Fisher*) requires that Appellants provide more than a general statement of a diagnostic utility. Appellants have met this requirement, and have provided supporting extrinsic evidence in multiple different samples. Again, Appellants are not *claiming* a method of diagnosing all cancers, a method of diagnosing all types of breast cancers, or a method of detecting a normal cell by requiring the absence of elevated 2.2412 expression levels. Instead, Appellants have asserted that the polynucleotides encoding 2.2412 protein have utility in view of the differential expression of 2.2412.

Finally, Appellants note for the record that to the extent the present application may recite "candidate" or "potential" effector protein of the Grb7 family of signaling proteins, this is irrelevant to any asserted utility of the 2.2412 protein encoded by the polynucleotide recited in the present claims. It is not necessary to know whether 2.2412 protein modulates a signaling pathway involving Grb7 or and/or Grb14 in order to provide utilities based on the elevated expression of 2.2412 in certain cancerous cells or based on the specific binding of 2.2412 protein to Grb7 and to Grb14, which were known to exhibit elevated expression in certain cancer cells.

SUMMARY

Appellants respectfully request that the rejections of the claims under 35 U.S.C. §§ 101 and 112, ¶1 be reversed.

Respectfully submitted,
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